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Early Clinical Development of ARQ 197, a Selective, Non–ATP-Competitive Inhibitor Targeting MET Tyrosine Kinase for the Treatment of Advanced Cancers

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ABSTRACT

Expression of the receptor tyrosine kinase c-MET (MET, mesenchymal-epithelial transition factor) in many cancers, and its participation in multiple signal transduction pathways involved in malignant tumor growth, suggest a wide therapeutic potential for MET inhibition in human cancer. Here we describe the discovery and early clinical development of ARQ 197, a novel, selective, non–ATP-competitive inhibitor of MET. Phase I studies demonstrate that ARQ 197 has a predictable pharmacokinetics and favorable safety profile, making it a potentially ideal partner for combination with cytotoxic chemotherapies and targeted anticancer agents. Results from phase I and phase II trials demonstrate preliminary evidence of anticancer activity. New data from a global phase II randomized trial comparing a combination of ARQ 197 plus erlotinib with erlotinib/placebo, in endothelial growth factor receptor inhibitor-naïve patients with locally advanced/metastatic non–small cell lung cancer, demonstrate improvement in progression-free and overall survival with combined therapy. Results were especially pronounced for patients with non–squamous lung cancer histologies, and in particular molecularly defined subgroups including KRAS mutations. These and other data from ARQ 197 clinical trials in hepatocellular, germ-cell, pancreatic (in combination with gemcitabine), and colorectal (in combination with cetuximab and irinotecan) cancers further highlight the potential role of ARQ 197 in existing and emerging anticancer therapeutic regimens. ***The Oncologist*** 2011;16:788–799

INTRODUCTION

A growing body of evidence establishes the role of c-MET (mesenchymal-epithelial transition factor; MET), a receptor tyrosine kinase encoded by the proto-oncogene, *c-MET*, in a wide variety of cancers, including colon, gastric, bladder, breast, ovarian, pancreatic, lung, and hematologic malignancies [1–4]. Once MET is bound by its high affinity ligand, hepatocyte growth factor (HGF; also known as scatter factor), the MET signaling pathway is activated and involved in a variety of

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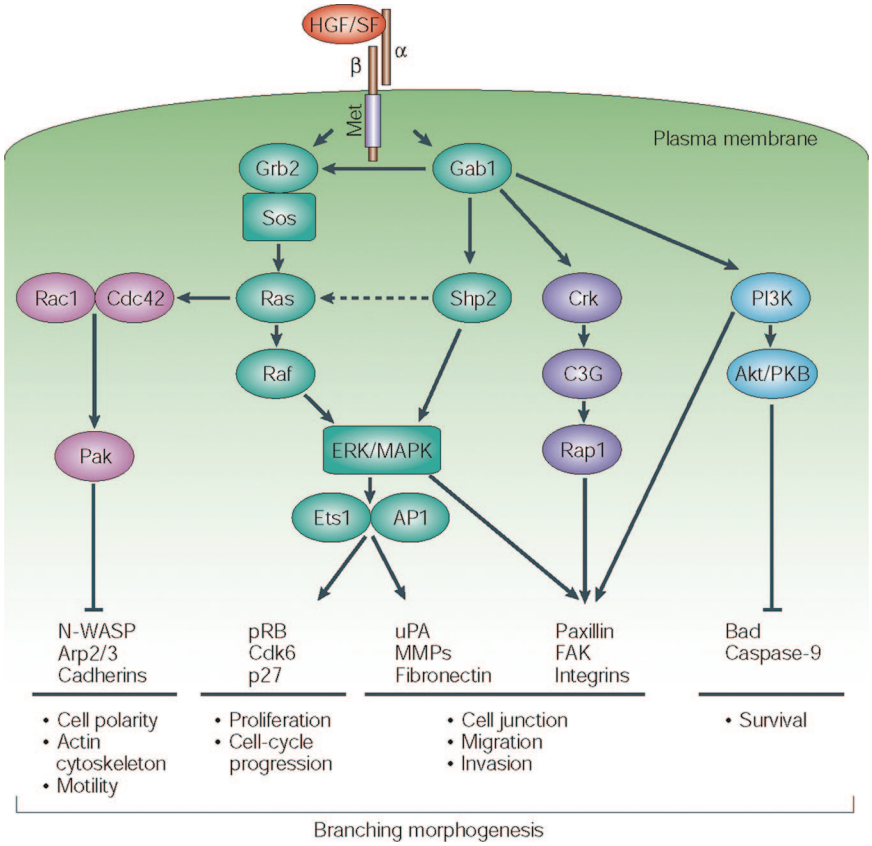

Figure 1. Schematic representation of HCG/MET signaling pathway [3]. Activation of MET results in the recruitment of scaffolding proteins such as Gab1 and Grb2, which activate Shp2, Ras, and ERK/MAPK. Abbreviations: ERK/MAPK, extracellular signal–regulated kinase/mitogen-activated protein kinase; Gab1, growth factor receptor–bound protein 2 (Grb2)-associated binder 1; HGF/SF, hepatocyte growth factor/scatter factor; MET, mesenchymal-epithelial transition factor; Pak, p21-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; PKB, protein kinase B; Shp2, SH2 domain–containing protein tyrosine phosphatase 2; SH2, Src-homology-2; Sos, son-of-sevenless; α and β, subunits of the receptor that are present after proteolytic cleavage. Adapted by permission from Macmillan Publishers Ltd. Birchmeier C, Birchmeier W, Gherardi E et al. Metastasis, motility and more. Nat Rev Mol Cell Biol 2003;4:915–925.

physiologic processes with direct or indirect involvement in oncogenesis (Figure 1) [3]. These include angiogenesis, tumor cell proliferation, survival, migration, resistance to apoptosis, aggressive cellular invasion, and metastasis [1–3].

MET expression may be dysregulated in a number of human cancers, resulting in an augmented response to HGF [5]. Furthermore, genetic aberrations can lead to aberrant *c-MET* signaling, with germline and sporadic mutations, gene amplification, and overexpression described across a wide spectrum of tumor histologies [6].

MET overexpression and mutated *c-MET* appear correlated with poor clinical prognosis [3, 5, 7]. Tumors that depend on MET signaling for growth, differentiation, and/or maintenance are described as being "addicted" to MET [8]. Relevant tumors dependent on the HGF/MET axis are thought to include the majority of hereditary and sporadic papillary renal cell carcinomas (RCCs) [9], gastric cancer [10, 11], multiple myeloma [12], and glioblastoma multiforme [13]. A subset of lung, colon, ovary, pancreas, and head and neck cancers also harbor dysregulated MET (including its overexpression, constitutive activation, gene amplification, ligand-dependent activation, or mutation) [14–16].

Recent evidence suggests that acquired resistance to epithelial growth factor receptor (EGFR) inhibitors in certain cancers may be achieved through *c-MET* gene amplification, in turn leading to MET hyperactivation and MET-dependent phosphorylation of HER3 [8, 17]. Phosphorylated HER3 recruits phosphoinositide 3-kinase (PI3K) and stimulates PI3K-based survival pathways, causing resistance to EGFR inhibitors. Conversely, inhibition of MET signaling in these resistant cells may potentially restore sensitivity to EGFR inhibitors. It is further hypothesized that simultaneous blockade of MET and EGFR may impair growth in these tumor cells [8, 16, 17].

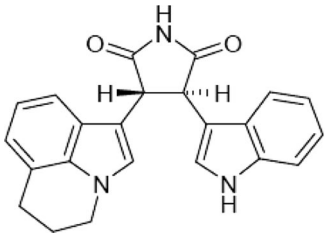

Figure 2. Chemical structure of ARQ 197 [18].

EARLY DEVELOPMENT

Pharmacologic Profile

In Vitro Studies

ARQ 197 (chemical formula (−)-(3*R*,4*R*)-3-(5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-4-(1*H*-indol-3-yl)pyrrolidine-2,5-dione) (Figure 2) is the most advanced agent in a new class of *trans*-3,4-bisubstituted pyrrolidine-2,5-diones [18]. Among >230 human protein kinases tested, ARQ 197 concentrations of 5–10 μM selectively inhibit only MET to any appreciable extent (Figure 3) [18, 19]. ARQ 197 binds to an inactive, or nonphosphorylated, conformation of MET and locks it in this inactive state [20]. Kinetic analyses of ARQ 197 demonstrate high in vitro potency (inhibitory constant [K_i] $\approx$ 35.5 nM) and a non–ATP-competitive mechanism of action, which may explain a high degree of kinase selectivity that distinguishes the compound from other MET inhibitors [18, 21, 22]. ARQ 197 inhibits both constitutive and ligand-mediated MET autophosphorylation in different human cancer cell lines, with a 50% inhibitory concentration (IC50) of 100–300 nM (Table 1), in turn inhibiting downstream MET effectors Akt, Erk-1/2, and STAT-3 [18]. Maximal MET inhibition is achieved by 24 hours, and it can be sustained for up to 8–12 hours following withdrawal of ARQ 197, demonstrating prolonged durability of MET kinase receptor inhibition [23]. ARQ 197 also inhibits HGF-induced phosphorylation of MET (IC50 $\approx$ 0.1 μM) and HGF-induced downstream targets, such as ERK1/2, MEK1/2, and FAK [18].

In Vivo Studies

Xenograft mouse models using several human cancer cell lines demonstrate marked antitumor activity with orally administered ARQ 197 200 mg/kg, as indicated by significant tumor growth reductions ranging from 45% to 79% (all P values <0.05) in colon, gastric, breast, prostate, and pancreatic cancer models [18, 24, 25]. Compared with control animals, the level of phospho-MET was dramatically reduced in immunosuppressed mice with established HT-29 human colon cancer 24 hours after administration of a single oral dose of ARQ 197 (200 mg/kg) [18]. Moreover, tumor xenografts were exposed to sustained ARQ 197 plasma levels following a single oral dose of 200 mg/kg in mice, consistent with concentrations shown to inhibit MET enzymatic activity and proliferation of MET-harboring cancer cell lines in vitro. ARQ 197 plasma levels 10 hours after dosing were 1.3 μM—greater than threefold above the ARQ 197 K_i for MET [18]. ARQ 197 also demonstrated the ability to prevent bone metastases in a humanized mouse model of metastatic breast cancer [24], as well as significant inhibition of liver metastases in murine xenograft models of human cancer [25].

Preclinical Pharmacokinetics and Metabolism

Studies of individual human cytochrome (CY) P450 isozymes demonstrate that ARQ 197 is rapidly metabolized by CYP2C19 (half-life [$t_{1/2}$] = 2.8 minutes) and moderately metabolized by CYP3A4 ($t_{1/2}$ = 16.3 minutes) [26]. ARQ 197 does not appear to be a strong inhibitor of any of the major CYP450 enzymes tested [26]. Metabolic studies in rat, dog, mouse, and human hepatocytes indicate that oxidative biotransformation is the primary metabolic pathway [26]. On the basis of pharmacokinetic (PK) data, oral bioavailability was ≥20% in the species investigated: mouse, rat, and dog [26].

CLINICAL DEVELOPMENT

Pharmacokinetic Data

Evaluation of ARQ 197 PK parameters was performed for studies ARQ 197-101, ARQ 197-103, ARQ 197-111 (with erlotinib), ARQ 197-114, ARQ 197-204, ARQ 197-116 (with sorafenib), and ARQ 197-117 (with gemcitabine) [27–34]. Across these studies, ARQ 197 was administered at doses ranging from 10 to 480 mg twice daily (bid). Additionally, in most studies, several active pharmaceutical ingredient (API) forms were used, including amorphous, crystalline A, and crystalline B. The different API forms were encountered as the API manufacturing process was scaled to larger batch size. Ultimately, crystalline B was determined to be the most stable and is currently being dosed in patients at 360 mg bid (the proposed phase II dose at the time of this publication). In general, across studies, exposure (area under the plasma concentration time curve [AUC] and maximum plasma concentration [Cmax]) was highly variable but generally increased as the dose was increased. In most cases, however, the resulting increase in exposure was less than dose proportional. In a recent study in which patients were dosed 360 mg bid with crystalline B ARQ 197, on day 1, mean Cmax (n = 8) was 1,766 ± 1,452 ng/ml and mean AUC(0–12) was 14,053 ± 13,736 h*ng/

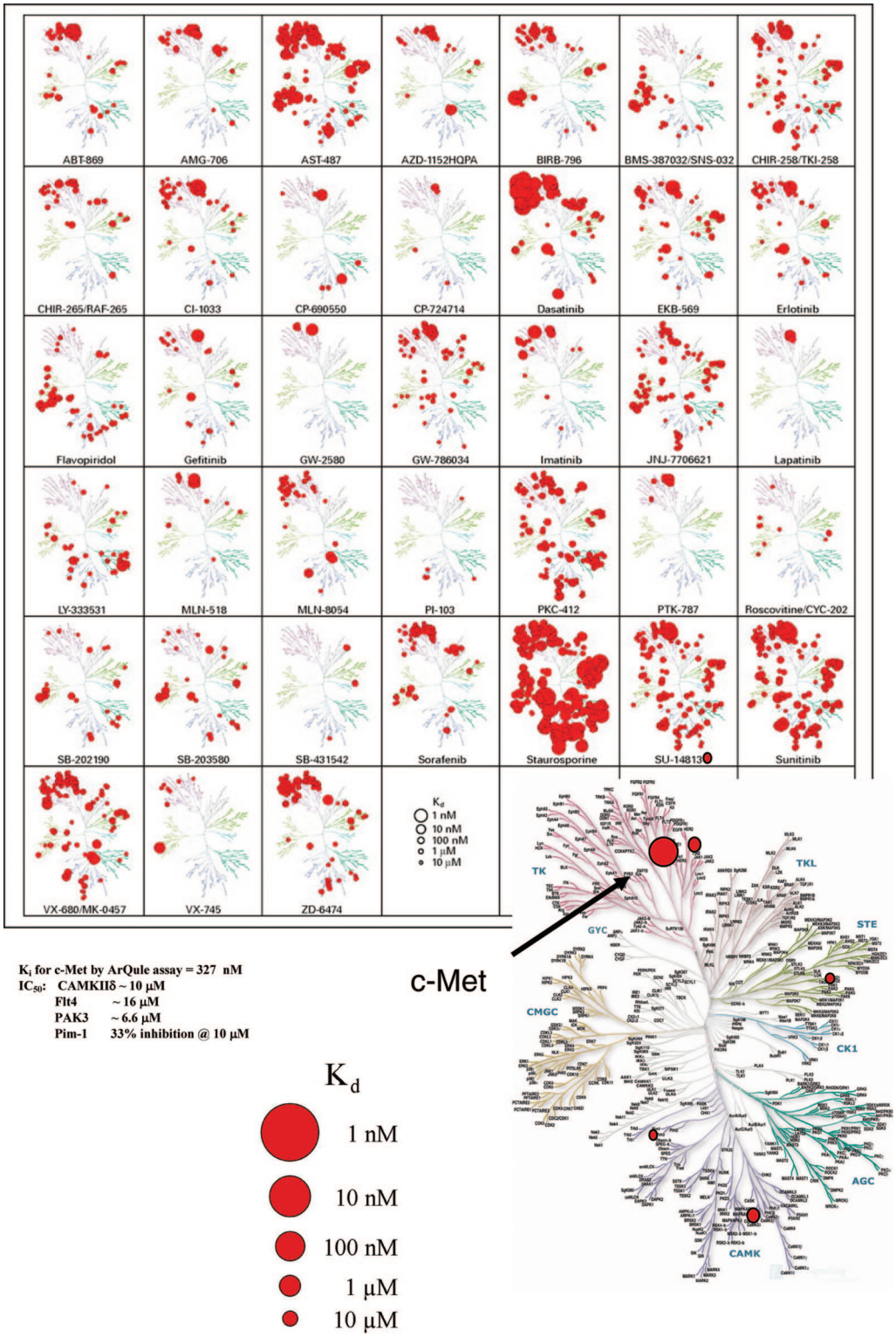

Figure 3. Kinase specificity of ARQ 197 [18]. The inhibitory effect of ARQ 197 was profiled against 230 human kinases. The size of the red circles on the kinome tree are proportional to the potency determined by repeat dose-response follow-up inhibition studies against the top five kinases inhibited by ARQ 197. Abbreviations: IC50, 50% inhibitory concentration; K_i, inhibitory constant; MET, mesenchymal-epithelial transition factor. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (http://www.cellsignal.com).

Table 1. MET status and ARQ 197 IC50 values for 12 evaluated human cancer cell lines

Human cancer cell line	Tumor origin	MET status	Cytotoxic IC50 (μM)
SK-MEL-28	Melanoma	−	>33
NCI-H661	NSCLC	−	>33
NCI-H446	SCLC	−	7.00
MDA-MB-231	Breast cancer	+	0.55
DLD-1	Colon cancer	+	0.53
A549	NSCLC	+	0.59
SK-OV-3	Ovarian cancer	+	0.66
NCI-H460	NSCLC	+	0.60
A375	Melanoma	+	0.42
NCI-H441	NSCLC	+	0.30
HT29	Colon cancer	+	0.49
MKN-45	Gastric cancer	+	0.58

Abbreviations: IC50, 50% inhibitory concentration; MET, mesenchymal-epithelial transition factor; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer. Adapted with permission from the American Association for Cancer Research: Munshi N, Jeay S, Li Y et al. ARQ 197, a novel and selective inhibitor of the human c-Met receptor tyrosin kinase with anti-tumor activity. Mol Cancer Ther 2010;9:1544–1553.

ml. On day 29, mean Cmax ($n = 6$) was 1,986 ± 1,487 ng/ml, and mean AUC(0–12) was 15,003 ± 13,428 h*ng/ml [35]. In general, mean values for $t_{1/2}$ and apparent clearance remained relatively constant up to the maximum tolerated dose (MTD). In combination therapy (with erlotinib, sorafenib, or gemcitabine), ARQ 197 exposure (and adverse event [AE] profile) appears similar to that reported for monotherapy studies and indicates the absence of drug-drug interactions [26–33].

Phase I and II Studies

Monotherapy ARQ 197-101: Phase I Dose-Escalation Study in Metastatic Solid Tumors (USA)

Initiated in 2006, ARQ 197-101 was a phase I dose-escalation study of ARQ 197 in 74 patients with metastatic solid tumors [30–32]. The two dosing schedules evaluated, one intermittent and one continuous, demonstrated favorable safety profiles, with no dose-limiting toxicities (DLTs) observed and no MTD identified [30, 32]. The most common (≥5%) drug-related AEs included fatigue (16.2%), nausea (13.5%), vomiting (6.8%), and diarrhea (5.6%).

A total of 61 patients were evaluable for response by Response Evaluation Criteria In Solid Tumors (RECIST) 1.0 criteria [31]. Among these, three patients (5%; one each with neuroendocrine, prostate, and testicular cancer) achieved a partial response (PR), 38 patients (62%) demonstrated stable disease (SD), and 20 (33%) patients experienced progressive disease (PD). Disease control (complete response + PR + SD) was achieved in 41 of the evaluable patients (67%) [31].

ARQ 197–103: Phase I Dose-Escalation Study in Advanced Solid Tumors (U.K.)

Because no MTD was identified in the earlier phase I trial, an additional phase I trial, ARQ 197-103, was initiated in 2007 [27, 33]. Fifty-one patients were assigned to one of five continuous 28-day cycle dosing cohorts: 100 ($n = 3$), 200 ($n = 6$), 300 ($n = 23$), 360 ($n = 15$), and 400 ($n = 4$) mg bid.

In the 200 mg bid cohort, one DLT of grade 3 fatigue was observed, which resolved <24 hours after drug cessation. In the 400 mg bid cohort, a DLT of grade 3 febrile neutropenia was observed in each of two patients; in one of these patients, two other grade 3 DLTs were observed (mucosal inflammation and palmar-plantar erythrodysesthesia). All DLTs resolved within 2 weeks of ARQ 197 discontinuation [33]. ARQ 197 300 mg bid was initially identified as the MTD but was subsequently adjusted to 360 mg bid following introduction of a modified commercial-grade formulation and PK studies demonstrating a 5:6 conversion factor [33]. Safety of the 360 mg bid dose using the modified formulation was confirmed in an expanded cohort of 20 patients [29, 36]. In total, 51 patients experienced 73 drug-related AEs, with gastrointestinal AEs ($n = 18$; 25%) and fatigue ($n = 10$; 14%) reported most frequently [33].

Regarding efficacy, SD by RECIST 1.0 was the best observed response for 14 patients (27%), demonstrating evidence of tumor regression [33]. Tumor response was also examined using dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI) and diffusion weighted-MRI imaging of lesions of interest. Preliminary DCE-MRI data showed nonstatistically significant changes in mean and median transfer constant after 7 days of ARQ 197 treatment, suggesting only a possible antiangiogenic effect of the drug.

ARQ 197-114: Phase Ib Study in Cirrhotic Patients with Hepatocellular Carcinoma

ARQ 197-114 is a recently conducted multicenter, single-cohort, Phase Ib study evaluating safety/toxicity of ARQ 197 in Child-Pugh A or B cirrhotic patients with hepatocellular carcinoma (HCC) who received two or fewer prior systemic chemotherapy regimens (last treatment completed at least 4 weeks before the first dose of ARQ 197) [28, 37, 38]. As of March 19, 2010, a total of 21 patients (19 male, 2 female; mean age 70 years) were

treated with ARQ 197 at the recommended phase II dose of 360 mg bid [28, 37, 38].

Drug-related AEs were reported in 20 patients (95.2%), with the most commonly reported drug-related AEs of any grade being anemia (43%), asthenia (43%), neutropenia (38%), leukopenia (33%), diarrhea (29%), anorexia (29%), and fatigue (24%). Study drug-related serious adverse events (SAEs) were observed in four patients (19%), including grade 3 anemia ($n = 2$), grade 4 neutropenia ($n = 2$), grade 4 leukopenia ($n = 1$), grade 5 pneumonia ($n = 1$), and sepsis ($n = 1$). No drug-related worsening of liver function was observed [38].

Preliminary antitumor activity of ARQ 197 was observed among 16 patients evaluable for tumor response. Progression-free rates at 2 and 4 months were 59.7% and 39.8%, respectively. Median time on study was 13 weeks, and median time to progression was 15.3 weeks. One patient remained with SD for >13 months, with a decrease in tumor density observed by computed tomography scan [38].

Tumor biomarker analyses revealed that all patient biopsies were positive for total MET and at least weakly positive for HGF. Of particular note is that plasma biomarker analyses suggest that neutropenia may have correlated with reductions in plasma HGF (and to a lesser extent with reductions in MET levels) and, in turn, tumor response. Conversely, plasma vascular endothelial growth factor levels did not appear to correlate with ARQ 197 activity [38].

ARQ 197-204: Phase II Monotherapy Study in Patients with Microphthalmia Transcription Factor–Associated Tumors

ARQ 197-204 is a recently completed phase II trial evaluating ARQ 197 as monotherapy in patients with a rare set of microphthalmia transcription factor–associated tumors, including translocation-associated RCC, alveolar soft-part sarcoma (ASPS), and clear cell sarcoma (CCS) [34]. Patients aged 13 years or older were initially administered oral ARQ 197 120 mg bid, and the protocol was subsequently amended to increase the dose to 360 mg bid following identification of the phase I MTD [34].

As of June 1, 2009, 36 patients (mean age, 26.5 years; 8 with CCS, 19 with ASPS, and 9 with RCC) were evaluable for efficacy analysis [39]. A PR was observed in 1 patient with CCS, whereas SD was observed in 21 total patients (15 with ASPS, 3 with CCS, and 3 with RCC). The disease control rate was 79% in patients with ASPS versus 50% and 33% in those with CCS and RCC, respectively. Median progression-free survival (PFS) was 37 and 8 weeks in patients with ASPS and CCS, respectively. These data are difficult to interpret given the paucity of existing historical benchmarks for efficacy but are intriguing given the extremely poor prognosis of these tumor types. Further development opportunities are being explored.

Regarding safety, the most common drug-related AEs observed here were fatigue (46%), nausea (41%), and vomiting (34%). Two drug-related SAEs of grade 3 febrile neutropenia were observed in a patient treated with ARQ 197 360 mg bid.

ARQ 197-215: Phase II Monotherapy Study in Patients with Unresectable HCC (ClinicalTrials.gov Identifier: NCT00802555)

On the basis of results of the Phase Ib ARQ 197-114 study, a phase II clinical trial evaluating ARQ 197 monotherapy in HCC is currently underway and enrolling patients [40]. ARQ 195-215 is a global, randomized, double-blind, placebo-controlled, phase II clinical trial in patients who experienced disease progression following—or who were unable to tolerate—one prior line of systemic chemotherapy. Approximately 99 patients with Child-Pugh A status will be enrolled from multiple study sites. The primary study endpoint is median time to progression; secondary endpoints include overall survival (OS), disease control rate, and biomarker analyses (including circulating MET and HGF levels).

ARQ 197-A-U251: Phase II Study in Patients with Relapsed/Refractory Germ Cell Tumors (ClinicalTrials.gov Identifier: NCT01055067)

ARQ 197 is currently being investigated in a multicenter phase II study in patients with relapsed/refractory germ cell tumors. No proven therapies currently exist in this extremely difficult-to-treat patient population. The primary objective of this monotherapy trial is to determine the objective response and progression-free rates following four cycles of ARQ 197 360 mg bid [41].

Combination Therapy

ARQ 197-111: Phase I Dose-Escalation Study in Combination with Erlotinib in Advanced Solid Tumors

This phase I dose-escalation trial evaluated the combination of ARQ 197 (administered at 120 [$n = 8$], 240 [$n = 4$], and 360 mg bid [$n = 20$]) and the EGFR inhibitor erlotinib (150 mg once daily [qd]) in patients with advanced solid tumors [29, 36]. Intrapatient dose escalation was allowed in the absence of DLTs through one cycle of therapy (21 days). The combination was well tolerated,

with fatigue (28.1%), nausea (18.8%), and rash (18.8%) being the most commonly observed AEs, and primarily grade 1–2 in severity [36]. Two patients experienced drug-related SAEs: neutropenia at 360 mg bid and sinus bradycardia at 240 mg bid [29]. DLTs were observed in two patients at 360 mg bid (grade 4 neutropenia in one patient, and grade 4 neutropenia and leukopenia and grade 3 thrombocytopenia in the other); all events resolved after treatment discontinuation. In the absence of a formally identified MTD, 360 mg bid was selected as the ARQ 197 recommended phase II dose (RP2D) for subsequent phase II combination studies with erlotinib at its full approved dose of 150 mg daily [36].

ARQ 197-116: Phase I Dose-Escalation Study in Combination with Sorafenib in Advanced Solid Tumors (ClinicalTrials.gov Identifier: NCT00827177)

This ongoing phase I dose-escalation trial is evaluating the safety and tolerability of ARQ 197 administered in combination with sorafenib [35, 42]. An initial cohort was treated with ARQ 197 360 mg bid + sorafenib 200 mg bid (dose level 1 [DL1]). Because no DLTs were observed, dosing was increased to the full single-agent doses of both drugs: ARQ 197 360 mg bid + sorafenib 400 mg bid (dose level 2 [DL2]). Intrapatient dose escalation was allowed, and an extension cohort was opened following determination of the RP2D, with planned enrollment of up to 50 patients with RCC, HCC, breast cancer, non–small-cell lung cancer (NSCLC), and melanoma [35].

As of April 2, 2010, 22 patients were enrolled and treated at the two dose levels (5 at DL1, 9 at DL2, and 8 at the RP2D). A total of 81 AEs considered related to either or both drugs were reported in 20 of 22 patients (90.9%), with the most commonly reported drug-related AEs of any grade being fatigue (36.4%), diarrhea (27.3%), anorexia (22.7%), and rash (22.7%). No DLTs were reported at DL1, and 1 of 9 patients (11.1%) at DL2 experienced two DLTs (grade 3 fatigue and grade 3 dyspnea) [35, 42].

As of May 5, 2010, 14 of 18 patients (77.8%) evaluable for efficacy by RECIST 1.1 demonstrated a best response of SD for 7+ to 32+ weeks (median 12+ weeks) [35]. All 7 evaluable patients with RCC experienced SD for 7+ to 31+ weeks (median 15+ weeks); 4 of 5 patients with HCC experienced SD for 8+ to 24+ weeks (median 15+ weeks); and 3 of 6 evaluable patients with other tumors experienced SD for 8–32 weeks (median 8 weeks). These results suggest that combined inhibition of MET and angiogenic signaling may have therapeutic potential [35]. Further development plans are being discussed.

ARQ 197-117: Phase I Dose-Escalation Study in Combination with Gemcitabine in Advanced Solid Tumors (ClinicalTrials.gov identifier: NCT00874042)

This ongoing multicenter, dose-escalation phase Ib study conducted in patients with advanced solid tumors is examining the safety and tolerability of competitive doses (120–360 mg bid) and schedules (either continuous or interrupted) of ARQ 197 given in combination with gemcitabine (1000 mg/m^2 ¾ weekly) [43]. To date, no DLTs have been observed with intermittent ARQ 197 dosing, and all 21 patients initially enrolled are now being entered into the continuous dosing cohorts. AEs considered to be at least possibly drug-related were reported in 52% of patients, with the most commonly observed AEs including neutropenia (33%), thrombocytopenia (24%), anemia (19%), fatigue (14%), leukopenia (10%), and anorexia (10%). To date, one patient experienced a drug-related SAE (anemia), and one non–drug-related death was reported [43]. On the basis of the favorable safety profile, phase II combination studies are being considered in several indications.

ARQ 197-209: Phase II Combination Study with Erlotinib Versus Erlotinib/Placebo in Metastatic NSCLC

ARQ 197-209 is a recently concluded global, randomized, placebo-controlled, double-blind phase II clinical trial that evaluated erlotinib + ARQ 197 compared with erlotinib + placebo in second-/third-line chemotherapy-experienced, EGFR-inhibitor–naïve patients ($N = 167$) with inoperable, locally advanced/metastatic NSCLC [36, 44]. Eligible patients were randomly assigned to receive erlotinib 150 mg qd + ARQ 197 360 mg bid ($n = 84$), or erlotinib 150 mg qd + placebo ($n = 83$; 28-day cycles in both groups) [36, 44]. The primary study endpoint was PFS.

Results presented at the 2010 Annual Meeting of the American Society of Clinical Oncology demonstrated that median time on therapy was 101 days in the combination arm versus 65 days in the erlotinib/placebo arm. Treatment discontinuation occurred in 71 (85%) and 74 (89%) patients, respectively, primarily due to PD (50 [60%] vs 58 [70%] patients, respectively). In the intention-to-treat population ($N = 167$), PFS was prolonged with the ARQ 197/erlotinib combination versus erlotinib/placebo (16.1 vs 9.7 weeks). The hazard ratio (HR) for progression was statistically significant when adjusting for imbalances in the treatment arms using a prespecified Cox regression model (HR = 0.68; 95% confidence interval [CI]: 0.47, 0.98; $P < 0.05$). This improvement in PFS was paralleled by a similar improvement in median OS (36.6 vs 29.4 weeks). PFS and OS benefits were most pronounced in patients with non–squamous-cell histology ($n = 117$), with a 9.2-week im-

Table 2. Evaluation of erlotinib/ARQ 197 versus erlotinib/placebo in patients with advanced NSCLC

Outcome	Erlotinib + ARQ 197 ($n = 84$)	Erlotinib + placebo ($n = 83$)	Adjusted HR (95% CI)	p
Median PFS by investigator assessment, weeks	16.1	9.7	0.68 (0.47–0.98)	<.05
Nonsquamous histology	18.9	9.7	0.61 (0.47–0.98)	<.05
Median OS, weeks	36.6	29.4	0.88 (0.6–1.3)	.52
Nonsquamous histology	43.1	29.4	0.58 (0.34–0.99)	<.05
Response, %				
PR	10	7		
SD	56	47		
Disease control	66	54		

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

provement in median PFS (18.9 vs 9.7 weeks) and a 13.7-week improvement in median OS (43.1 vs 29.4 weeks). These hazard ratios were statistically significant when adjusting for key prognostic factors: 0.61 (95% CI: 0.47, 0.98; $P < 0.05$) for PFS and 0.58 (95% CI: 0.34, 0.99; $P < 0.05$) for OS. Analyses of specific biologic subgroups showed benefits of the ARQ 197/erlotinib combination in patients with MET FISH gene copy number >4, *EGFR* wild-type status, and *KRAS* mutation status.

Of intriguing interest, furthermore, was evidence demonstrated in this clinical trial of ARQ 197's potential antimetastatic effect. Among intention-to-treat patients, median time to new metastatic lesions was increased from 3.6 months in the erlotinib–placebo arm to 7.3 months in the combination arm (HR 0.49; 95% CI: 0.31, 0.78). This effect was even more pronounced in non–squamous-cell patients, among whom median time to metastatic disease was increased from 3.6 to 11.0 months (HR 0.46; 95% CI: 0.26, 0.82) [45].

RECIST PRs were observed in 7/73 evaluable patients (10%) in the ARQ 197/erlotinib arm compared with 5/72 evaluable patients (7%) in the erlotinib/placebo arm. SD was observed in 41 (56%) and 34 (47%) patients, yielding disease control rates of 66% and 54%, respectively (Table 2) [44].

Thirty-four patients in the erlotinib/placebo arm were offered crossover to the ARQ 197/erlotinib arm at the time of progression, and 23 of these patients were evaluable for a postprogression response. Two patients (8.7%) demonstrated a PR, 9 (39.1%) demonstrated SD, and 12 (52.2%) had PD as their best response per RECIST 1.0.

Overall, there were no clinically relevant or statistically significant differences in AE rates between treatment and control arms. The most common AEs included rash, diarrhea, anorexia, anemia, and fatigue and were generally grade 1/2 in severity. Rates of neutropenia for the ARQ 197/erlotinib and erlotinib/placebo arms were 6% and 4%, respectively [36, 44]. On the basis of these results, the sponsors are currently planning a global phase III trial of ARQ 197 and erlotinib as second-/third-line treatment in patients with metastatic non–squamous-cell grade 3/4 NSCLC.

ARQ 197-A-U252: Phase I/II Combination Study with Irinotecan and Cetuximab in Metastatic Colorectal Cancer (ClinicalTrials.gov: NCT01075048)

This ongoing phase I/II, randomized, placebo-controlled clinical trial is evaluating ARQ 197 in combination with irinotecan/cetuximab in patients with metastatic CRC and wild-type *KRAS* status who have progressed on front-line systemic therapy [46]. Recently, the safety, tolerability, and RP2D of the ARQ 197/irinotecan/cetuximab combination were established in the phase I stage of this trial, and a phase II stage comparing the study treatments for PFS began enrollment.

Additional Studies

Additional phase I–III studies, evaluating safety of ARQ 197, as monotherapy or in combination with erlotinib, and efficacy of ARQ 197 in NSCLC and gastric cancer (ClinicalTrials.gov identifier: NCT01152645) are being planned or performed in Japan by Kyowa Hakko Kirin Co., Ltd.

Future and Planned Studies

Future Phase I Studies

A Children's Oncology Group–led phase I dose-escalation trial of ARQ 197 in children with advanced tumors is expected to begin accrual in 2011. On the basis of the favorable safety profile observed in the phase I combination studies of ARQ 197 with gemcitabine and sorafenib in patients with advanced solid tumors, phase II combination studies with these agents are being planned. Other ARQ

Table 3. Anticancer activity of ARQ 197 in phase I and II studies (monotherapy and combinations): Tumor reduction ≥20% or stable disease for ≥6 months [36, 39, 46]

Trial/ patient no.	ECOG/ Karnofsky	Tumor type	Baseline tumor size (mm)	Best tumor dec (%)	Stage	No. prior surgeries	No. prior chemo-biologic therapies	Weeks on study	Best response
197-101-001	100%	Neuroendocrine tumor (prostate)	125.0	−37.6	UNK	2	1	32	PR
197-101-006	90%	Angiomyolipoma	190.0	−13.2	III	4	12	23	SD
197-101-007	90%	Pancreatic cancer	25.0	−4.0	IV	2	3	103	SD
197-101-008	90%	Prostate cancer	162.0	−38.9	IV	6	4	29	PR
197-101-020	80%	Renal cell cancer	98.0	−14.8	IV	2	3	35	SD
197-101-022	80%	Testicular cancer	85.0	−32.9	III	1	12	65	PR
197-101-027	80%	Thyroid cancer (papillary)	73.7	−5.7	IV	5	0	107	SD
197-101-028	80%	Renal cell cancer	74.3	−5.1	IV	9	2	54	SD
	90%	Liposarcoma	145.0	8.3	II	1	1	42	SD
197-101-032	90%	Sarcoma NOS	168.0	−5.3	II	9	3	47	SD
197-101-038	100%	Thyroid cancer (papillary)	138.6	7.3	IV	4	0	39	SD
197-101-052	90%	Metastatic papillary adenocarcinoma of unknown primary	29.0	−3.8	IV	2	3	39	SD
197-103-011	2	Melanoma (eye)	366.0	−4.6	NA	1	3	34	SD
	0	Chondrosarcoma	240.0	3.7	NA	3	6	24	SD
197-111-001	0	NSCLC	35.0	−2.8	IIB	2	2	27	SD
197-111-003	0	NSCLC	31.0	−19.4	IV	4	4	35	SD
197-111-012	1	Chordoma	50	0.0	I	1	0	106	SD
197-111-013	1	Ovarian	129	−2.3	III	0	8	36	SD
197-111-018	1	NSCLC	30	−3.3	IV	2	3	81	SD
197-111-021	1	NSCLC	35	8.6	IV	1	3	57	SD
197-111-024	1	Microcystic adnexal carcinoma	12	−33.3	Unknown	8	0	29	PR
197-111-032	1	NSCLC	28	−14.3	IV	2	5	63	SD
197-111-033	1	Squamous-cell carcinoma	30	0.0	Unknown	3	4	30	SD
197-114-002	0	Hepatocellular carcinoma	12	−16.7	IV	2	2	69	SD
197-114-020	0	Hepatocellular carcinoma	58	−20.7	IV	3	1	28	SD
197-116-001	1	Renal cell carcinoma	187	−12.3	IV	0	0	31	SD
197-116-002	0	Adenocarcinoma of rectum	155	0	IV	5	8	36	SD
197-116-006	0	Renal cell carcinoma	104.8	−22.4	IV	6	0	31	SD
197-116-008	0	Recurrent hepatocellular carcinoma	187	−3.7	IV	4	0	32	SD
197-116-011	0	Hepatocellular carcinoma	272.3	−0.1	IV	0	3	40	SD
197-116-014	0	Renal cell carcinoma	39.2	−6.9	IV	0	2	31	SD
197-116-015	0	Renal cell carcinoma	90	−21.8	IV	0	4	23	SD
197-116-021	0	Renal cell carcinoma	161.5	−24.3	IV	2	3	24	SD
197-116-022	1	Melanoma	35.9	−37.1	IV	0	2	15	PR
197-117-003	1	Adenocarcinoma of uterus/ovary	34	−77.1	IV	1	1	19	PR
197-117-006	0	Breast cancer	55	−100	IV	1	4	23	PR
197-117-007	0	Endometrial adenocarcinoma	27	−44.4	IV	3	4	31	PR
197-117-008	1	NSCLC	133	−55.6	IV	0	3	48	PR
197-117-020	0	Metastatic ovarian cancer to lymph nodes	51	−23.5	IV	3	7	31	SD
197-117-024	1	Pancreatic	126	−21.4	IV	5	0	25	SD
197-117-028	1	NSCLC with liver metastases	47	−51.1	IV	2	2	24	PR
197-117-033	0	Adenocarcinoma of ovary	40	−52.5	IIIB	2	9	16	PR
197-117-053	0	Cholangiocarcinoma	16	−31.3	IV	0	0	16	PR
197-204-006	0	ASPS	144.0	−1.9	IV	0	4	73	SD
197-204-010	0	Clear cell sarcoma	47.7	−45.3	IIB	2	5	44	PR
197-204-023	0	Translocational-associated RCC	28.2	2.1	III	5	4	40	SD

(continued)

Table 3. (continued)

Trial/ patient no.	ECOG/ Karnofsky	Tumor type	Baseline tumor size (mm)	Best tumor dec (%)	Stage	No. prior surgeries	No. prior chemo-biologic therapies	Weeks on study	Best response
197-204-027	0	ASPS	170.2	−1.0	IV	1	2	40	SD
197-204-034	0	ASPS	24.0	−10.0		1	1	60	SD
197-204-036	1	Clear cell sarcoma	89.0	0.0		2	0	34	SD
197-204-044	0	ASPS	286.0	4.2		1	2	30	SD
197-209-003	1	NSCLC	31	−16.6	IV	0	1	40	SD
197-209-025	1	NSCLC	52	−13.5	IIIB	0	2	52	SD
197-209-057	1	NSCLC	31	−16.1	IV	1	1	41	SD
197-209-064	1	NSCLC	33	−3.0	IV	0	4	44	SD
197-209-066	1	NSCLC	87	−3.4	IIIB	1	1	32	SD
197-209-079	1	NSCLC	98	8.2	IV	1	1	40	SD
197-209-082	1	NSCLC	91	−6.6	IV	0	1	40	SD
197-209-091	1	NSCLC	114	−30.7	IV	0	1	36	PR
197-209-096	1	NSCLC	116	−39.7	IV	1	1	32	PR
197-209-112	1	NSCLC	101	−70.5	IV	0	1	32	PR
197-209-113	0	NSCLC	63	−81.0	IV	0	2	32	PR
197-209-119	1	NSCLC	34	−26.5	IV	0	1	30	SD
197-209-126	1	NSCLC	84	−21.4	IV	0	1	32	SD
197-209-141	1	NSCLC	94	−66.0	IV	1	2	28	PR
197-209-142	1	NSCLC	269	−24.9	IV	0	2	28	SD
197-209-147	0	NSCLC	110	−41.8	IV	0	1	28	PR
197-209-148	1	NSCLC	44	−65.9	IV	0	1	28	PR

Abbreviations: ECOG, Eastern Collaborative Oncology Group; NOS, not otherwise specified; NSCLC, non–small cell lung cancer; PR, partial response; SD, stable disease.

197–based combinations currently being evaluated include those containing pemetrexed, vascular endothelial growth factor inhibitors, irreversible EGFR inhibitors, and mammalian target of rapamycin inhibitors. Many of these combinations are included in the National Cancer Institute's Cancer Therapy Evaluation Program clinical development plan for ARQ 197.

Molecular-Guided Trials

A series of carefully targeted ARQ 197 trials are being planned in lung cancer and other metastatic malignancies based on a variety of disease biomarkers. These include plans to investigate ARQ 197 in NSCLC patients with *KRAS*-mutation–positive lung cancer. It is anticipated that these focused analyses of ARQ 197 efficacy and safety, in both monotherapy and/or combination therapy, will define those targeted patient subgroups most likely to benefit from treatment with ARQ 197.

Conclusion

ARQ 197 is a novel, selective, non–ATP-competitive inhibitor of the receptor tyrosine kinase c-MET, a key mediator of oncogenic signaling implicated in multiple stages of tumor progression, in a wide variety of human cancers. ARQ 197 demonstrates efficacy in both in vitro preclinical models and multiple human cancer xenograft models. In the clinic, ARQ 197 has been orally administered to >400 cancer patients and demonstrates favorable safety and predictable PK profiles.

Results from phase I studies additionally demonstrate favorable safety profiles for ARQ 197 in combination with erlotinib, sorafenib, and gemcitabine. Across all studies, the most commonly reported drug-related AEs appear to be fatigue and nausea. The most frequent drug-related SAEs, which are hematologic in nature, appear manageable and consistent with the involvement of MET in the maturation of bone marrow progenitor cells.

Data from both phase I and II clinical trials evaluating ARQ 197 across multiple tumor types demonstrate the promising anticancer activity of ARQ 197 achieved through selective inhibition of the MET signaling pathway. Patients with notable tumor reduction or long periods of stable disease are included in Table 3. Of particular clinical relevance are recent data from a global randomized trial in second-/third-line NSCLC, where the combination of ARQ 197 and erlotinib resulted in notable improvements in PFS and OS, as well as provocative increases in the time to new metastatic disease. Further data from ongoing and planned phase I–III clinical trials will determine whether ARQ 197 can influence current cancer treatment paradigms as a sin-

gle agent or through its inclusion in multidrug anticancer regimens.

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